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TYPE A BEHAVIOR PATTERN: SOME OF ITS PATHOPHYSIOLOGICAL COMPONENTS*

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EVER since 1958, when we first detected the extraordinarily close association of Type A behavior pattern† with increased prevalence of clinical coronary heart disease,[1] we have been attempting to identify the particular pathophysiological mechanisms which serve as the immediate pathogenic processes whereby the emotional traits comprising Type A behavior hasten the course of coronary atherosclerosis and probably also the onset of coronary thrombosis, infarction, and sudden death.

Dr. C. J. Van Slyke in 1958 suggested that the specific emotion-action complex which we had observed in coronary patients be called Type A

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†Type A behavior pattern is an action-emotion complex that is exhibited by those individuals who are engaged in a *chronic and incessant* struggle to achieve more and more in less and less time (thus giving rise to a sense of time urgency or "hurry sickness"[2]) and who also usually (but not always) exhibit a free-floating but well-rationalized hostility. Detection of the pattern cannot be accomplished by any self-administered questionnaire of which I am aware, because of the rationalizations of these individuals and their extraordinary reluctance to admit to any type of behavior less than meritorious.

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behavior pattern. He thought such an appellation might not so readily affront those psychiatrists who previously had not looked too kindly on our applications for federal grants dealing with this subject. "*After all,*" he said, "you really are describing only that which you see, the *behavior* of your patients. Such a description I don't believe will annoy the psychiatrists reviewing your grant applications." In retrospect, I believe Dr. Van Slyke was partly but not completely correct in his prophecy.

It has not been and still is not easy to detect or identify these possible intermediate pathogenic mechanisms. This is so primarily, I believe, because the pathogenesis of coronary heart disease, unlike that of an acute infectious disorder or even a neoplasm, is a process that probably begins (in Western man at least) in late childhood or early adolescence, as Osler once described it,[3] "creeping on slowly but surely, *'with no pace perceived,"* and does not strike until the fifth or sixth decade. From the onset of our own studies we knew that we were confronted by a disorder whose exact pace could not be perceived. However, in the beginning our interest was primarily to detect and identify an abnormal biochemical or biophysical process in these coronary-prone Type A subjects, not necessarily to determine the pace at which this process wreaked its havoc.

Aware, then, of the relatively slow progress of coronary atherosclerosis, from the onset we enrolled for our pathophysiological studies only those Type A subjects who appeared to exhibit the pattern in its most extreme or intense form (we have designated such individuals as Type A-1, in contradistinction to Type A-2, or less afflicted subjects). Conversely, we enrolled as controls for the same studies only those Type B subjects who appeared to exhibit complete tranquility and total peace of mind (we designated such individuals as Type B-4 in contradistinction to Type B-3, or slightly less serene subjects). Our rationale for always selecting these extreme subjects could be understood by recalling how much easier it is to detect the deleterious hemodynamic effects of hypertension in subjects whose average blood pressure is 250/130 mm. Hg than in those whose average blood pressure may be only 155/95 mm. Hg.

Also, we have executed almost all our studies on Type A and B subjects during their weekday working periods. We have done this because, if the incessant struggles of Type A subjects make them prone to the early onset of clinical coronary heart disease, they should be investigated when they are in the milieu that invites, initiates, sustains, or demands such struggle. Indeed, when Type A subjects can identify nothing in their environment to

ignite either their sense of time urgency or hostility, they frequently slip into Type B behavior.

I have described these two features of our research studies on Type A subjects because to date only those observers who likewise have studied extreme Type A and B subjects and also have done so in their usual working environment have been able to confirm completely all phases of our studies.

In our many studies of still-healthy Type A subjects we have tended to concentrate on measuring the physiological or biochemical phenomena that have been observed to have gone awry in patients already suffering from clinical coronary heart disease.

Pathophysiological Phenomena Observed to Date in the Majority of Severe Type A Subjects

Cholesterol metabolism. Even before we had completely formulated all the components of the Type A behavior pattern we already had the clearcut impression (obtained from a survey of both businessmen and physicians[4] that persons chronically exposed to and reacting to deadlines might be more susceptible to infarctions than persons not so exposed. Because of this impression, we first studied the cholesterol content and clotting propensity of the blood of men before, during, and after they had encountered a deadline of great importance to them. These men were accountants; their deadline was the April 15th tax deadline for the completion and dispatch of the tax forms of their clients. We decided to do measurements of serum cholesterol and blood clotting because these two phenomena were and continue to be suspected of complicity in the pathogenesis of coronary heart disease.

The results of this initial study[5] showed that when these men approached this deadline date, although no change had occurred earlier either in their diet or exercise patterns, their average serum cholesterol rose and their clotting time hastened. I believe this study presented the first unequivocal demonstration of the fact that an emotional stimulus could alter the serum cholesterol level in man. But despite the fact that this finding has been confirmed repeatedly by many investigators,[6-10] there still remain some epidemiologists who appear ineluctably tied to the view that the serum cholesterol level is governed almost exclusively by dietary or genetic influences.

The finding of a hastened clotting time in our subjects as they struggled to finish their tax forms merely confirmed the observations that Cannon had made[11] 40 years earlier of the blood-clotting proclivities of an animal during struggle or conflict.

Following this study of accountants, we studied a group of Type A men who, unlike our accountants, were almost always involved in deadlines. Again, the results[1] left little doubt that men who are chronically involved in a severe struggle with time exhibit a significantly higher serum cholesterol and a faster clotting time than men not so afflicted with a sense of urgency. Nor was there any sex protection against the hypercholesterolemia induced by an incessant sense of time urgency and struggle since when women oppressed by the same traits were studied,[12] their average serum cholesterol was elevated also.

But several caveats about these studies. First, all these Type A subjects, as already mentioned, were severely oppressed by a sense of time urgency. Second, although the average serum cholesterol of the entire group of Type A subjects invariably was greater than that of the control Type B subjects, not all Type A subjects exhibit hypercholesterolemia (just as all coronary patients do not exhibit this phenomenon). Of course, the completely tranquil Type B subject almost never exhibits hypercholesterolemia (i.e., a serum cholesterol level above 250 mg./100 ml.). In other words, whenever a subject exhibits a serum cholesterol level above 250 mg./100 ml., but still below 400 mg./100 ml., he usually will be found to exhibit Type A behavior.

In a later study[13] we found that most Type A subjects who were hypercholesterolemic usually exhibited hyperlipoproteinemia of Type III or IV. However, I should add that most subjects that I have encountered who exhibit a Type II hyperlipoproteinemia also almost always exhibit Type A behavior. If these observations and correlations prove to be correct, elevated levels of serum cholesterol might best be lowered not solely by diet and drugs but also by attempted alteration of Type A behavior. I do not know of any multimillion-dollar epidemiological effort presently embodying this approach. Failure to recognize this possible effect of behavior pattern upon serum cholesterol values may reduce the significance of results obtained in some presently conducted studies aimed at reducing the serum cholesterol by dietary means alone.

Triglyceride and fatty acid metabolism. We also observed[14] that the average fasting and postprandial serum triglyceride levels, like the serum

cholesterol levels, of severely afflicted Type A subjects were greater than those of Type B subjects. Indeed, we rarely detected a fasting serum triglyceride exceeding 100 mg./100 ml. in a Type B subject.

Conversely, we usually found that the serum triglyceride level of most Type A subjects exceeded the latter value. Indeed, it probably has been the inclusion of many Type A subjects in studies of so-called normal groups of subjects that has resulted in the widely held belief that even a fasting serum triglyceride of 150 mg./100 ml. may be normal. In our experience, a fasting serum triglyceride above 125 mg./100 ml. must be considered abnormally high.

As might be expected from the above results, we also observed[14] that the majority of severe Type A subjects also exhibited prolonged postprandial hypertriglyceridemia. Hyperchylomicronemia usually accompanied this hypertriglyceridemia.[14]

Peculiarly perhaps, we never were able to detect a significant difference in the levels of serum fatty acid of Type A and B subjects.

Postprandial sludging of erythrocytes. Almost all of the Type A subjects we studied who reacted to a fat meal with severe hypertriglyceridemia also showed[14,15] marked sludging of their erythrocytes (as visualized in their bulbar conjunctival circulation) during and even a number of hours after the period of maximal hyperlipemia, i.e., during the first eight hours after ingestion of a meal rich either in animal or vegetable fat. Such sludging probably also takes place in the coronary circulation of these susceptible subjects. Indeed, the occurrence of this phenomenon could explain the onset of angina pectoris and electrocardiographic abnormalities sometimes observed[16] in coronary patients after ingestion of a fat-rich meal.

In our studies[14,15] it was obvious that this type of sludging took place only in those Type A subjects who also exhibited postprandial lipemia. Once this sludging did appear after the intake of fat it might persist, as I have already mentioned, for many hours after the ingestion of a single fat-containing meal. Thus, if these subjects ingest fat in several meals it is probable that they harbor myriad masses of sludged erythrocytes in the capillary circulation of various organs and tissues for perhaps the greater part of a 24-hour day. At this writing I know of no single phenomenon that has been so consistently neglected in the study of coronary heart disease as this one. Later we may rue this inexcusable oversight.

Catecholamine metabolism. If a simple method of measuring small quan-

tities of various catecholamines in biological samples had been available a few decades ago, the possible relation between norepinephrine or some other adrenergic hormone and the occurrence of coronary heart disease would attract almost as much investigative attention as cholesterol now does; the potential artery-damaging and thrombogenic propensities of some catecholamines (in particular norepinephrine) are well recognized.[17-19] However, even at present, the measurement of small quantities of either norepinephrine or epinephrine in biological samples is not a simple procedure, although recently Diamant and Byers[20] have described a relatively simple yet precise method whereby levels of both epinephrine and norepinephrine in plasma can be measured in quite small samples (10 ml. or less) of blood.

Type A subjects, while not suffering from any fixed error in the metabolism of either epinephrine or norepinephrine, nevertheless secrete more norepinephrine during working hours[21] and also during any individual competitive activity[22] than Type B subjects. These findings have been directly confirmed by Carruthers.[23] Also, Hames et al.,[24] studying coronary-prone subjects, and Nestel et al.,[25] studying patients already suffering from angina pectoris, found that the majority of these persons excreted an excessive amount of catecholamines.

Do these data unequivocally imply a functionally deranged metabolism of catecholamines in the pathogenesis of coronary heart disease? Of course they do not, yet, the more I study both the coronary-prone Type A subject and the coronary patient himself, the more I find myself entertaining the thought that one or more of the adrenergic hormones probably does play an important role in increasing the rate of coronary atherogenesis. More succinctly stated, I strongly suspect that if the chronic hypersecretion of moderate quantities of catecholamines could be eliminated, clinical coronary heart disease might be much less frequent in the fifth and sixth decades of life than it now is.

The peculiar corticotropin responses of most severe type A subjects. We have observed three peculiar phenomenona related to corticotropin dynamics in Type A subjects.

First, we noted more than 10 years ago[26] that the administration of corticotropin to Type A subjects exhibiting preprandial and postprandial hypertriglyceridemia promptly alleviated the condition. This effect, however, could not be duplicated by cortisone.[27] The last observation at first glance suggested that the hypolipemic effect of corticotropin might be

due to some direct effect of corticotropin itself upon fat metabolism. But this was disproved when the administration of corticotropin to Addisonian patients failed to alleviate their hyperglyceridemia. Apparently, then, the fat-clearing effect of corticotropin that we observed in our Type A subjects must have been due to adrenocorticotropic hormone (ACTH) inducing hypersecretion of some adrenal hormone other than cortisone. Unfortunately, we have not been able to reproduce this singular hypolipemic property of corticotropin in the rat or rabbit. Because of this failure we have not been able to pursue our investigation of this truly astonishing property of ACTH.

The second peculiar corticotropin-related phenomenon that we observed in most severe Type A subjects was their relatively poor adrenal response to the injection of this hormone. Thus, whereas our Type B subjects uniformly responded to an injection of ACTH with an average sixfold increase in urinary excretion of 17-hydroxycorticosteroids (17-HOCS), no such response was observed in our Type A subjects. Thus, 40% of our Type A men either did not respond to the injection of ACTH at all or exhibited a markedly diminished response in their urinary excretion of 17-hydroxycorticosteroids.

The third peculiar corticotropin phenomenon we observed in Type A subjects was their increased serum level of ACTH throughout the waking day.[29] This last finding makes one wonder whether the above observed failure of so many severely afflicted Type A subjects to increase their adrenal 17-HOCS output after the injection of ACTH might not be due to the chronic increased discharge of ACTH of these subjects as shown by the elevated serum levels of this pituitary hormone.

Growth hormone metabolism. As far as we can tell, most severely afflicted Type A men exhibit a deficit not only in their fasting levels of serum growth hormone,[30] but also a diminished growth hormone response to the infusion of arginine.[31] More recently, after we had observed the necessity of the presence of growth hormone for the normal regulation of serum cholesterol,[32] we administered human growth hormone to six moderately hypercholesterolemic Type A subjects. The serum cholesterol was lowered in all.[33]

Why do the majority of severely afflicted Type A subjects exhibit a reduced serum level of growth hormone and a diminished response to the infusion of arginine? I suspect that these persons do not lack the capacity to produce and discharge growth hormone in normal quantities, but rather

they catabolize this hormone at a faster rate than most Type B subjects. However, a 24-hour monitoring of the serum growth hormone levels of these persons will be necessary to answer this question with certainty.

When it is remembered that approximately half or more of a contemporary urban group of men will exhibit Type A behavior[34] our finding of a reduced fasting serum level of growth hormone in this type of individual may well explain why other investigators[35] previously have observed that only about half of all men tested show a significant fasting level of this hormone.

Hyperinsulinism. Although almost all Type A subjects under the age of 60 years display normal preprandial and postprandial glucose values in plasma, the majority of well developed Type A subjects exhibit[30] a hyperinsulinemic response to the ingestion of glucose. Although our data have indicated clearly enough that this hyperinsulinemia was not responsible for the hypertriglyceridemia so often observed in these subjects, the same data suggested that the hypertriglyceridemia possibly had played a causal role in the pathogenesis of the hyperinsulinemia.

The Experimental Production of Neurogenic Hypercholesterolemia

In 1958, when we first observed in our study of accountants[5] the waxing and waning of their serum cholesterol levels depending respectively on the intensification and relaxation of their emotional state, we suspected that sooner or later we would be able to alter the serum cholesterol in experimental animals by interference with hypothalamic function. This experimental induction of hypercholesterolemia finally was accomplished by us in 1969[36] when, after electrolytic injury of the ventral medical nucleus, the fornix, and the medial portion of the lateral hypothalamic nucleus of the rat, the serum cholesterol level promptly began to rise.

Subsequent studies have indicated that this hypothalamic variety of hypercholesterolemia is not due to derangement in the hormonal metabolism of the pituitary, thyroid, adrenal, or testes. Indeed, this kind of hypercholesterolemia occurs as readily in the hypothalamus-injured rat without its pituitary, thyroid, adrenal, and sex glands as in the intact rat.[37] The fundamental error responsible for this kind of neurogenic hypercholesterolemia appears to be a relative inability of the liver to remove cholesterol (particularly chylomicron cholesterol) from the blood stream.[38,39] Just how and why a lesion of the hypothalamus leads to this hepatic insuffi-

ciency now occupies much of our attention, since we believe that an elucidation of the pathogenesis of this type of very low-density hyperlipoproteinemia[40] may reveal the nature of the process at work in and responsible for many cases of Type IV hyperlipoproteinemia in man.

Concluding Remarks

If a new concept is to survive and prevail it must be capable of enduring and surmounting all the strictures that may be mounted against it. Approximately 17 years have elapsed since we first announced the close association of the Type A behavior pattern and the prevalence of coronary disease. During these 17 years our concept certainly has received its share of criticism. But as far as I know, none of the results obtained in our various clinical and epidemiological studies has been contradicted by results obtained from other studies oriented toward the same problems and carried out in comparable fashion. Indeed, as a result of our own clinical[14,21,22,30,31] and epidemiological[41,42] studies, as well as the epidemiological[43-46] and clinical[47,48] studies of other investigators, the Type A behavior pattern now is accepted as a significant coronary risk factor by perhaps a majority of practicing cardiologists. These physicians seemingly have little difficulty in observing the extremely high prevalence of this type of behavior in their coronary patients.

At present several extremely expensive epidemiological studies are being conducted to determine whether eradication or modification of certain risk factors—cigarette smoking, cholesterol-rich diet, and hypertension—may reduce the incidence of coronary disease. Some day, we may hope, attempts will be made to modify or eradicate the Type A behavior pattern in patients who have already suffered an infarction, and to observe if the recurrence of an infarction will occur significantly less often in those patients who have succeeded in altering their behavior pattern than in those patients whose Type A behavior pattern has been left intact.

Coronary patients exhibiting Type A behavior rather than normal individuals exhibiting Type A behavior should be selected first for such a study for several reasons. First, because the recurrent infarction is so much commoner than initial infarction in normal but perhaps high risk subjects, a much smaller cohort of patients can be chosen than is now being done in studies in which high risk but noncoronary subjects are being followed. Second and most important, it has been not too difficult to modify the behavior of a goodly number of postinfarction patients, whereas I have

found it almost impossible to modify the behavior of a Type A individual who has no coronary symptoms. Of course, it there ever comes a time when all physicians are convinced that Type A behavior is not only one of the several coronary risk factors but also one of the most important factors, perhaps many Type A subjects may be induced to alter their behavior even before they suffer their first infarction. However, such total medical consensus does not appear imminent.

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